UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,020	12/31/2001	Yuchua Li	5051-451IP	8515

20792 7590 02/23/2004

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,020	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,35-50 and 55-61* is/are pending in the application.

4a) Of the above claim(s) *5,23,26-38,44-47 and 51-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-22,24,25,39-43 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04/01; 9/03/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-4, 6-22, 24-25, 37-41 and 46-50 in the Paper filed 12-05-03 is acknowledged. The traversal is on the ground(s) that the Examiner has not demonstrated that the requirements for claim restriction have been met. Applicants cite the criteria for restriction as per MPEP § 803. This is not found persuasive because the grounds for restriction set forth by the examiner in the Election/Restriction requirement mailed 11-05-03 were on the basis that the claims of the instant application were drawn to inventions or groups which are not linked as to form a single general inventive concept under PCT Rule 13.1. Applicants did not address the grounds for the lack of unity of invention set forth by the examiner in the initial restriction requirement mailed 11-05-03.

It is also noted that claims 37-38 and 46-47 were inappropriately assigned to Group I, and claims 42-43 were incorrectly assigned to Group II, in the Election/Restriction requirement mailed 11-05-03. Claims 37-38 and 46-47 are drawn to antisense-based inhibitors and methods of use, and should have been assigned to Group II. Therefore, since Applicants elected Group I, drawn to peptide based inhibitors of mucus secretion and methods of use, claims 37-38 and 46-47 are considered part of a non-elected invention and therefore will not be examined with the remaining claims set forth in the elected invention of Group I. Conversely, claims 42-43 are drawn to pharmaceutical formulations comprising a peptide-inhibiting fragment of MARCKS, and should have been assigned to Group I. Claims 42-43 will be examined with the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 5, 23, 26-38, 44-47, and 51-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 11-05-03.

3. Applicants have cancelled claims 26-34, 51-54, and 62-66 without prejudice or disclaimer in the Paper filed 6-06-02. Therefore, claims 1-25, 35-50, and 55-61 are currently pending in the instant application. However, only claims 1-4, 6-22, 24-25, 39-43 and 48-50 are currently under examination.

Priority

4. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 7-11, 13-20, 22, 25, 39, 41-43, and 48-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims are broadly drawn to a method of inhibiting mucus secretion by a mucus-secreting cell, comprising administering to said cell a mucus-inhibitory amount of a compound that inhibits MARCKS protein-related mucus secretion. The compounds encompassed by the claimed invention include an active fragment of a MARCKS protein, and any other compound that functions to inhibit MARCKS protein-related mucus secretion.

The specification as filed teaches that the MA-PSD peptide functions to increase MARCKS-related mucus secretion when administered to a mucus-secreting cell (see page 9, lines 14-28), and that the MANS-peptide functions to inhibit the release of mucin granules and the secretion of mucus in mucus secreting cells (p. 19, lines 5-14). Both the MANS-peptide and the MA-PSD peptide are both fragments of the MARCKS protein, however the influence of these peptide fragments on MARCK-related mucus secretion is completely opposite. Therefore, simply because Applicants recite that the peptide inhibitors used in the claimed methods comprise from about 10 to about 50 contiguous amino acids from SEQ ID NO: 3, this

information is not sufficient to describe functional activity of the peptides used in the claimed methods. The actual functional activity of the peptide must be determined empirically.

MPEP § 2163[R-1] states" The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

In the instant case, since it is necessary to perform additional experimentation in order to determine if a putative compound functions to inhibit MARCKS mucus secretion, and furthermore to determine the amount of compound to be administered to a mucus-secreting cell to inhibit mucus secretion in said cell, it is concluded that Applicants were not in possession of the full scope of compounds encompassed by the instant claims. Neither the prior art, nor the specification as filed provides a specific correlation between the structure of the compounds of the present invention and its ability to function to inhibit mucus secretion.

7. Claims 1-4, 6-22, 24-25, 27-32, 37-41, and 46-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting mucus secretion in a cell comprising the administration of the MARCKS derived peptide according to SEQ ID NO: 1, and for stimulating mucus secretion by the administration of the MARCKS derived peptide according to SEQ ID NO: 2 of the instant application, does not reasonably provide enablement for inhibiting mucus secretion in cells by any other peptide besides the peptide according to SEQ

ID NO: 1 (MANS peptide), or for using the peptide according to SEQ ID NO: 2 (MA-PSD peptide) for inhibiting mucus secretion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification as filed clearly teaches that the MA-PSD peptide functions to increase MARCKS-related mucus secretion when administered to a mucus-secreting cell (see page 9, lines 14-28), and that the MANS-peptide functions to inhibit the release of mucin granules and the secretion of mucus in mucus secreting cells (p. 19, lines 5-14). Both the MANS-peptide and the MA-PSD peptide are both fragments of the MARCKS protein, however the influence of these peptide fragments on MARCK-related mucus secretion is completely opposite. Therefore, simply because Applicants recite that the peptide inhibitors used in the claimed methods comprise from about 10 to about 50 contiguous amino acids from SEQ ID NO:3, this information is not sufficient to describe functional activity of the peptides used in the claimed methods. The actual functional activity of the peptide must be determined empirically. Furthermore, Applicants are claiming methods of inhibiting and stimulating mucus secretion in a subject that requires in vivo efficacy for enablement purposes. However, Applicants have only provided one example of a peptide that functions in vitro to inhibit mucus secretion, that being the MANS peptide. Furthermore, Applicants have only provided one example of a peptide fragment of a MARCKS protein that stimulates mucus secretion, that being the MA-PSD peptide. The method recited in claim 1 of the instant application reads on the use of any and all peptides in this method of mucus secretion, there is no reference to a particular peptide for use in this method. The specification as filed does not sufficiently describe a representative number of

peptides that are capable of functioning in either stimulating mucus secretion of inhibiting mucus secretion in a subject.

To practice the invention as claimed, the skilled artisan would have to resort to de novo experimentation in order to identify other peptide inhibitors or stimulators of MARCKS-related mucus secretion, determining the structure and the pharmacology of the identified peptide inhibitors and peptide stimulators, determining modes of delivery in a whole organism for all categories of peptide inhibitors such that MARCKS-related mucus secretion is inhibited and the desired secondary effect (inhibition or stimulation of mucus secretion in a subject) is obtained. The specification as filed provides no specific guidelines in this regard.

Therefore, in view of the lack of working examples of peptide inhibitors which function in vivo to inhibit mucus secretion, the breadth of the claims, the insufficient description of a representative number of peptide inhibitors or peptide stimulators, and the unpredictable behavior of peptides as observed by the opposite influences of the peptides according to SEQ ID NO: 1 and 2 on mucus section, the specification does not describe the method of inhibiting or increasing mucus secretion in a subject by the administration of peptides, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steel et al., McCool et al. and Nakamura et al. in view of Graff et al., Staddon et al. (US Patent No. 6,407,058 B1), and Ali et al.

The instant claims are broadly drawn to a method of inhibiting mucus secretion by a mucus-secreting cell, comprising administering to said cell a mucus-inhibitory amount of a compound that inhibits MARCKS protein-related mucus secretion. The compounds encompassed by the claimed invention include an active fragment of a MARCKS protein, and any other compound that functions to inhibit MARCKS protein-related mucus secretion.

Steel et al. teach that mucus secretion from airway epithelial secretory cells and goblet cells can be elicited by muscarinic receptor stimulation, and that this event is coupled to a PTX-

sensitive G protein and requires the activation of a phorbol ester-insensitive form of PKC. Moreover, Steel et al. teach that mucus plays a prominent role in the morbidity and mortality of every major obstructive airway disorders, and that a more complete understanding of mucus secretion regulation would help in identification of potential therapeutic targets (p. L236). Steel et al. demonstrate the relationship between mucus secretion and the role of PKC, specifically they observed that in the presence of an inhibitor of PKC, chelerythrine chloride (CC), mucus secretion (carbachol-activated HMWG secretion) is blocked.

McCool et al. teaches that PMA, Phorbol 12-myristate 13-acetate, is an activator of PKC activity. PMA has also been reported to stimulate mucin secretion from rat submandibular gland cells and from rabbit gastric mucosal explants (p. 491, abstract).

Nakamura et al. (See IDS 10/04/01, #13) teach that mucin-like glycoprotein secretion is mediated by cyclic-AMP and Protein Kinase C signal transduction. In one embodiment of this reference Nakamura et al. examined the effect of the PKC inhibitor calphostin C on mucin-like glycoprotein secretion from rat cornea. They observed that calphostin C completely inhibited the stimulation of mucin-like glycoprotein secretion (page 517, Table II and following paragraph).

However, neither of the above references teaches the relationship between MARCKS protein activity and PKC function in mucus secretion. Additionally, neither of the above references teaches peptide inhibitors of MARCKS protein.

Graff et al. teach that peptides derived from the 25 amino acids comprising the phosphorylation site domain of the MARCKS protein (identical to SEQ ID NO: 2 of the instant application, see page 14391, 1st col.), function to inhibit protein kinase C activity.

Staddon et al. teach that the MARCKS protein was the first major substrate identified for PKC. Moreover, Staddon et al. teach that if increased phosphorylation of MARCKS is observed, it can usually be inferred that activation of PKC has occurred (see page 5, lines 10-17).

Ali et al. teach that PMA functions in stimulating PKC phosphorylation of the MARCKS protein. Specifically, in the presence of PMA there was a two-fold increase in phosphorylation of the MARCKS protein (p. 194). Furthermore, Ali et al. discloses antibodies targeting the MARCKS protein (p. 190).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Steel et al. McCool et al. and Nakamura et al. with the teachings of Graff et al., Staddon et al. and Ali et al. in the design of a method for inhibiting mucus secretion by using an inhibitor of the MARCKS protein, since Steel et al., McCool et al. and Nakamura et al. teach the relationship between PKC and mucus secretion, Graff teaches the relationship between PKC and MARCKS protein and discloses peptides with PKC inhibitory activity, and Ali et al. and Staddon et al. teach the relationship between PKC and MARCKS protein activity, and discloses antibodies targeting the MARCKS protein. One of ordinary skill in the art seeking alternative methods for regulating mucin secretion, would have been motivated to target a down stream component of PKC activation since the prior art clearly teaches that the PKC plays a significant role in regulating mucin secretion, and the prior art clearly teaches that the MARCKS protein is a down stream effector of PKC signaling. Furthermore, Steel et al. teach that a more complete understanding of mucus secretion regulation would help in identification of potential therapeutic targets, therefore since MARCKS protein activity is influenced by two key components controlling mucus secretion, PMA and PKC (See McCool et al. and Ali et al.), it

would have been obvious to design modulators of MARCKS protein activity for modulating mucus secretion. One of ordinary skill in the art would have had a reasonable expectation of success in the design of this method since the prior art teaches that inhibitors of PKC function to inhibit mucous secretion, and activators of PKC function to stimulate mucus secretion, therefore one would have expected that inhibiting a downstream component of PKC signaling would also result in the inhibition of mucous secretion.

Therefore, the invention as a whole is prima facie obvious over Steel et al., McCool et al. and Nakamura et al. in view of Graff et al., Staddon et al. (US Patent No. 6,407,058 B1), and Ali et al.

Notice of References Cited

11. With the exception of the Staddon et al. reference, all references were previously forwarded to Applicants during the prosecution of parent application 09/256,154 or presently considered in Applicant's Information Disclosure Statements filed 10/04/01 or 9/03/02.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE